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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/321,655	05/28/1999	STANTON L. GERSON	CWR-7091NP	6848

26294 7590 11/16/2010

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
11/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/321,655	GERSON, STANTON L.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/24/2010 has been entered.

Amended claims 2-5 and new claim 7 are pending in the present application; and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, was withdrawn in light of Applicant's cancellation of claim 6.

Claim Objections

Claim 7 is objected to because the phrase "expressing SH2, SH3, and SH4" appears to be incomplete. Please note that SH2, SH3 and SH4 are names of hybridoma cell lines that secrete monoclonal antibodies that bind specifically to surface antigens of human mesenchymal stem cells. The examiner suggests the insertion of the term "surface antigens" following the term "SH4" in the above phrase to obviate this objection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Nolta et al. (Blood 86:101-110, 1995, Cited previously) as evidenced by Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and/or Prockop et al (US 2002/0168765).

Nolta et al. disclosed a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of a stroma generated by 4^{th} passaged human allogeneic bone marrow stromal cells prior to the plating of CD34 cells (Abstract, and column 1, page 102). **The utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture** (column 1, third paragraph, page 102), and it contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (Science 276:71-74, 1997; see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-

adherent cells. Furthermore, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and "**Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages**" (see the abstract).

Therefore, the bone marrow stromal cells that were passaged 4 times for transduction as taught by Nolta et al are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue; and that the utilized cell population can be considered to be homogeneous because it is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture. Additionally, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton,

and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Nolta et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction by vigorous flushing and plating the collected cells twice to eliminate adherent stromal cells (column 1, last paragraph, page 102).

Accordingly, the method taught by Nolta et al meets every limitation of the claims as broadly written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 09/24/2010 (pages 5-12) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicant argues basically that Nolta et al do not teach a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded as recited in currently amended claims; and that the claimed isolated, purified and then culturally expanded homogeneous population of mesenchymal stem cells is not the same as the cell population taught by Nolta et al. Applicant also refers the examiner to page 5, lines 1-12 of the instant specification that teach the preparation of a homogeneous population of mesenchymal stem cells as claimed; and the post-filing art of Majumdar et al (J. Cell. Phys. 178:57-66, July 1998) which showed the differences between isolated, purified mesenchymal stem cells and marrow-derived stromal cells (MDSCs). Additionally, Applicant further noted that the present specification

differentiates between MSCs and Dexter stroma which is the same as the MDSCs discussed by Majumdar et al. Accordingly, one skilled in the art would recognize that MSCs are a distinct cell population from the heterogeneous stromal cells discussed by Nolta et al. Applicant further argues that Prockop (Science 276:71-74, 1997) does not support the argument that mesenchymal stem cells have been isolated, purified, and culturally expanded since Prokop teaches that there are advantages to utilizing isolation and purification methods as opposed to the "crude procedure of Freidenstein" (page 72, col. 1, paragraph 3; and col. 2, paragraph 2).

First, it is noted that the instant specification teaches specifically that human mesenchymal stem cells can be isolated and prepared according to any method known in the art, **not necessarily limited only to the process of isolating, purifying, and expanding the marrow-derived mesenchymal stem cells in culture as described in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584** (see at least page 5, first paragraph). As written, **the claims also do not limit a homogenous population of human mesenchymal stem cells to be isolated, purified and culturally expanded by any particularly method.**

Second, as already set forth in the above rejection the bone marrow stromal cell population derived from bone marrow spicules (after passage no. 4) as taught by Nolta et al. is devoid of most hematopoietic cells (column 1, third paragraph, page 102) and containing mesenchymal stem cells or multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop. Furthermore, the terms “Mesenchymal stem cell” and “Marrow stromal cell” have been used interchangeably in the art as also

evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as mesenchymal stem cells or marrow stromal cells (MSCs) (paragraph 2); and "Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages" (see the abstract). **By passaging bone marrow stromal cells and collected adherent bone marrow stromal cells at the 4th passage for transfection from an initial split of subconfluent layers of primary stromal cells, Nolta et al in fact isolated, purified and culturally expanded bone marrow stromal cells or mesenchymal stem cells relative at least to collected bone marrow specimen and/or primary bone marrow stromal cell culture. Additionally, the utilized 4th passage cell population can be considered to be homogeneous because it is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture**. It is further noted that the dependency of claim 7 on independent claim 5 indicates clearly that the homogeneous population of human mesenchymal stem cells in claim 5 is not necessarily completely free of T and B lymphocytes, macrophages and endothelial cells.

Third, with respect to the post-filing art of Majumdar et al (J. Cell. Phys. 178:57-66, July 1998) which showed the differences between isolated, purified mesenchymal stem cells and marrow-derived stromal cells (MDSCs); it should be noted that **the MDSC cell population of Majumdar et al was prepared by a different protocol from that of Nolta et al.; and that the MDSC cells of Majumdar et al. are primary or**

passage 1 cell cultures and not passage 4 cell culture of Nolta et al. Additionally, **the differences seen by Majumdar et al are only for 2 specific cell populations prepared under specific isolation and culture conditions** as evidenced by the statement "**There are several possible explanations for the difference seen in the two cultures, including the methods established for isolation and culture expansion of the cells**. First, MSCs are isolated using Percoll (1.073 g/ml) density sedimentation, while MDSCs were cultured following Ficoll-Paque (1.077 g/ml) fractionation. The small difference in the densities between Percoll and the Ficoll-Paque solutions may be selective for distinct cell populatons" (page 63, right column, last paragraph).

Fourth, the instant specification states explicitly "**Dexter stroma, in addition to MSCs**, contains T and B lymphocytes, macrophages, dendritic cells and endothelial cells" (page 2, lines 7-8). Since **primary Dexter stroma** already contained MSCs, then **selected adherent human bone marrow stromal cell population that is taught by Nolta et al also contains enriched MSCs because it is depleted of hematopoietic cells**. Furthermore, the instant specification states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in Dexter stroma and FN enhanced transduction**" (page 13, lines 23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23). These statements indicate clearly that **a much**

less purified, much more heterologous Dexter stromal cells (passaged only once) was already shown to be at least functionally equivalent to hMSCs used in the present invention, let alone for the 4th passaged human allogeneic bone marrow stromal cells devoid of most hematopoietic cells taught by Nolta et al.

Fifth, in contrast to Applicant's above comment regarding to the Prockop reference, Prockop stated explicitly "Therefore, **we used MSCs, prepared as described by Friedenstein and others (5-10)**, from a line of transgenic mice expressing a mutated collagen gene (25)" (page 73, col. 1, middle of the second paragraph).

Sixth, it is also noted that the degree of homogeneity of a human mesenchymal stem cell population is also subjective. For example, Prockop et al (US 2002/0168765) taught that **a given mesenchymal stem cell population is far from being homogeneous** (see at least paragraphs 9-18). Sylvester et al (US 7,592,174) stated, "Despite the definitions ascribed to MSC populations by their *in vitro* differentiation capabilities, the mechanisms governing their proliferation and multi-lineage differentiation capacity have been poorly understood…**One of the greatest obstacles in the study of MSC biology is the heterogeneity of studied cell populations**…This heterogeneity may be explained by the hypothesis that **true "mesenchymal stem cells" (cells with the ability to self-renew and differentiate into multiple lineages) are only a small sub-population of the pool of cells termed MSCs**, and the remainder of the mixed population consists of cells at various stages of differentiation

and commitment....**There are no universally accepted antigenic determinants of MSC**" (col. 1, line 40 continues to line 16 of col. 2).

Accordingly, amended claims 3-5 are rejected under 35 U.S.C. 102(b) for the reasons set forth above.

Amended claims 2 and 4-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Wells et al. (Gene therapy 2:512-520, 1995) as evidenced by Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and/or Prockop et al (US 2002/0168765).

Wells et al. disclosed a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with a retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of **an autologous bone marrow stromal support containing adherent stromal cells depleted of hematopoietic cells and macrophages that were obtained between passages 3 and 5** (see at least Abstract and Materials and Methods, particularly pages 518-519). The utilized bone marrow stromal support contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop(Science 276:71-74, 1997; see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in

the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and "**Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages**" (see the abstract).

Therefore, the bone marrow stromal cells that were obtained between passages 3 and 5 for transduction as taught by Wells et al are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue; and that the utilized cell population can be considered to be homogeneous because it is **depleted of hematopoietic cells and macrophages**. Additionally, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Wells et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction (column 1, first full paragraph, page 519).

Accordingly, the method taught by Wells et al meets every limitation of the claims as broadly written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 09/24/2010 (pages 13-18) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Once again, Applicant argues basically that Wells et al do not teach a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded as recited in currently amended claims; and that the claimed isolated, purified and then culturally expanded homogeneous population of mesenchymal stem cells is not the same as the cell population taught by Wells et al. Applicant also refers the examiner to page 5, lines 1-12 of the instant specification that teach the preparation of a homogeneous population of mesenchymal stem cells as claimed; and the post-filing art of Majumdar et al (J. Cell. Phys. 178:57-66, July 1998) which showed the differences between isolated, purified mesenchymal stem cells and marrow-derived stromal cells (MDSCs). Additionally, Applicant further noted that the present specification differentiates between MSCs and Dexter stroma which is the same as the MDSCs discussed by Majumdar et al. Accordingly, one skilled in the art would recognize that MSCs are a distinct cell population from the heterogeneous stromal cells discussed by Wells et al. Applicant further argues that Prockop (Science 276:71-74, 1997) does not support the argument that mesenchymal stem cells have been isolated,

purified, and culturally expanded since Prokop teaches that there are advantages to utilizing isolation and purification methods as opposed to the "crude procedure of Freidenstein" (page 72, col. 1, paragraph 3; and col. 2, paragraph 2).

First, it is noted that the instant specification teaches specifically that human mesenchymal stem cells can be isolated and prepared according to any method known in the art, **not necessarily limited only to the process of isolating, purifying, and expanding the marrow-derived mesenchymal stem cells in culture as described in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584** (see at least page 5, first paragraph). As written, **the claims also do not limit a homogenous population of human mesenchymal stem cells to be isolated, purified and culturally expanded by any particularly method.**

Second, as already set forth in the above rejection **an autologous bone marrow stromal support depleted of hematopoietic cells and macrophages, and obtained between passages 3 and 5** by Wells et al contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (Science 276:71-74, 1997; see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms “Mesenchymal stem cell” and “Marrow stromal cell” have been used interchangeably in the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, “Bone marrow contains at least two kinds of stem cells, hematopoietic stem

cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and "**Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages**" (see the abstract). **By passaging bone marrow stromal cells and collected adherent bone marrow stromal cells between passages 3 and 5 for transfection from an initial split of subconfluent layers of primary stromal cells, Wells et al in fact isolated, purified and culturally expanded bone marrow stromal cells or mesenchymal stem cells relative at least to collected bone marrow specimen and/or primary bone marrow stromal cell culture. Additionally, the utilized cell population between passages 3 and 5 can be considered to be homogeneous because it is depleted of hematopoietic cells and macrophages**. It is further noted that the dependency of claim 7 on independent claim 5 indicates clearly that the homogeneous population of human mesenchymal stem cells in claim 5 is not necessarily completely free of T and B lymphocytes, macrophages and endothelial cells.

Third, with respect to the post-filing art of Majumdar et al (J. Cell. Phys. 178:57-66, July 1998) which showed the differences between isolated, purified mesenchymal stem cells and marrow-derived stromal cells (MDSCs); it should be noted that **the MDSC cell population of Majumdar et al was prepared by a different protocol from that of Wells et al.; and that the MDSC cells of Majumdar et al. are primary or passage 1 cell cultures and not bone marrow stromal cell culture between passages 3 and 5 of Wells et al**. Additionally, **the differences seen by Majumdar et**

al are only for 2 specific cell populations prepared under specific isolation and culture conditions as evidenced by the statement "**There are several possible explanations for the difference seen in the two cultures, including the methods established for isolation and culture expansion of the cells**. First, MSCs are isolated using Percoll (1.073 g/ml) density sedimentation, while MDSCs were cultured following Ficoll-Paque (1.077 g/ml) fractionation. The small difference in the densities between Percoll and the Ficoll-Paque solutions may be selective for distinct cell populatons" (page 63, right column, last paragraph).

Fourth, the instant specification states explicitly "**Dexter stroma, in addition to MSCs**, contains T and B lymphocytes, macrophages, dendritic cells and endothelial cells" (page 2, lines 7-8). Since **primary Dexter stroma** already contained MSCs, then **selected adherent human bone marrow stromal cell population that is taught by Wells et al also contains enriched MSCs because it is depleted of hematopoietic cells and macrophages**. Furthermore, the instant specification states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in Dexter stroma and FN enhanced transduction**" (page 13, lines 23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23). These statements indicate clearly that **a much less purified, much more heterologous Dexter stromal cells (passaged only once) was already shown to be at least functionally equivalent to hMSCs used in**

the present invention, let alone for human autologous bone marrow stromal cells between passages 3 and 5, and depleted of hematopoietic cells and macrophages as taught by Wells et al.

Fifth, in contrast to Applicant's above comment regarding to the Prockop reference, Prockop stated explicitly "Therefore, **we used MSCs, prepared as described by Friedenstein and others (5-10)**, from a line of transgenic mice expressing a mutated collagen gene (25)" (page 73, col. 1, middle of the second paragraph).

Sixth, it is also noted that the degree of homogeneity of a human mesenchymal stem cell population is also subjective. For example, Prockop et al (US 2002/0168765) taught that **a given mesenchymal stem cell population is far from being homogeneous** (see at least paragraphs 9-18). Sylvester et al (US 7,592,174) stated, "Despite the definitions ascribed to MSC populations by their *in vitro* differentiation capabilities, the mechanisms governing their proliferation and multi-lineage differentiation capacity have been poorly understood…**One of the greatest obstacles in the study of MSC biology is the heterogeneity of studied cell populations**…This heterogeneity may be explained by the hypothesis that **true "mesenchymal stem cells" (cells with the ability to self-renew and differentiate into multiple lineages) are only a small sub-population of the pool of cells termed MSCs**, and the remainder of the mixed population consists of cells at various stages of differentiation and commitment….**There are no universally accepted antigenic determinants of MSC**" (col. 1, line 40 continues to line 16 of col. 2).

Accordingly, amended claims 3-5 are rejected under 35 U.S.C. 102(b) for the reasons set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Nolta et al. (Blood 86:101-110, 1995, Cited previously) or Wells et al. (Gene therapy 2:512-520, 1995) in view of Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and Caplan et al (US 5,486,359).

Nolta et al. disclosed a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of a stroma generated by 4^{th} passaged human allogeneic bone marrow stromal cells prior to the plating of CD34 cells (Abstract, and column 1, page 102). **The utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture** (column 1, third paragraph, page 102). Nolta et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction by vigorous

flushing and plating the collected cells twice to eliminate adherent stromal cells (column 1, last paragraph, page 102).

Wells et al. disclosed a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with a retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of **an autologous bone marrow stromal support containing adherent stromal cells depleted of hematopoietic cells and macrophages that were obtained between passages 3 and 5** (see at least Abstract and Materials and Methods, particularly pages 518-519). Wells et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction (column 1, first full paragraph, page 519).

Neither Nolta et al nor Wells et al teach specifically the use of a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue; **and wherein the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 antigens and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells**.

At the effective filing date of the present application (5/29/1998), Prockop already taught that **bone marrow stromal cells (MSC) can be isolated from other cells in marrow by their tendency to adhere to tissue culture plastic; and that the cells have many of the characteristics of stem cells for tissues that can roughly be defined as mesenchymal because they can be differentiated in culture into osteoblasts, chondrocytes, adipocytes, and even myoblasts** (see at least the

abstract). Prockop also noted that **the adherent cells used as feeder layers for HSCs have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of nonadherent cells** (page 72, column 3, bottom of first paragraph). Prockop also disclosed that experiments on the differentiation of MSCs have been carried out with **cultures of MSCs as described by the pioneering work of Friedenstein as well as by other groups that have attempted to prepare more homogeneous populations** (page 72, column 2, top of second paragraph; page 73, column 1, middle of second paragraph).

Additionally, at the effective filing date of the present application **Caplan et al also taught a method of isolating, purifying and culturing expanding human mesenchymal stem cells (hMSCs) from bone marrow, including a cell population having greater than 95% of human mesenchymal stem cells that express SH2, SH3 and SH4 antigens** (see at least the abstract; col. 1, line 65 continues to line 24 of col. 3; col. 4, lines 36-43). Caplan et al also disclosed **monoclonal hybridoma cell lines that synthesize and secrete monoclonal antibodies specific for human mesenchymal stem cells' SH2, SH3 and SH4 surface antigens; and that these monoclonal antibodies can also be used in the isolation of mesenchymal stem cells though various means** (col. 4, line 64 continues to line 9 of col. 5; col. 14, lines 45-57).

It would have been obvious for an ordinary skilled artisan to modify the teachings of either Nolta et al or Wells et al by also using at least a homogenous population of human bone marrow derived mesenchmal stem cells expressing uniformly SH2, SH3

and SH4 surface antigens, that has been isolated, purified and culturally expanded to support and/or increase gene transduction for human hematopoietic stem cells in light of the teachings of Prockop and Caplan et al as presented above.

An ordinary skilled artisan would have been motivated to carry out the above modification because Prockop already taught that **the adherent cells used as feeder layers for HSCs have many of the characteristics of bone marrow stromal cells that are characterized by their tendency to adhere to tissue culture plastic and are capable of differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts.** Moreover, an isolating and purifying method for a homogeneous population of human bone marrow mesenchymal stem cells expressing uniformly SH2, SH3 and SH4 surface antigens was also taught by Caplan et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Nolta et al or Wells et al; together with the teachings of Prockop and Caplan et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

WO 92/22584 disclosed similar teachings as those of Caplan et al (US 5,486,359).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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